

<붙임 4>

기관고유연구사업 최종보고서							
연구분야(코드)	LC0202	과제번호	1110550		지원 프로그램	창의과제	
과제성격(기초,응용,개발)	응용	실용화 대상여부	실용화	공개가능여부 (공개,비공개)			공개
연구과제명	(국문)조기위암환자에서 감시림프절생검을 이용한 비침습적 장기보존수술의 다기관 3상 연구 (영문)Multicenter phase III trial of sentinel node biopsy based minimally invasive organ preserving surgery in early gastric cancer patients						
과제책임자	소속	위암연구과	직위	책임연구원			
	성명	류근원	전공	외과			
세부과제	구분	세부과제명		세부과제책임자			
				성명	소속(직위)	전공	
	1						
	2						
	3						
총 연구기간	2011년 2월~ 2013년 12월(총 3년)		참여연구원수 (단위: 명, MY)		34		
연구기간 및 연구비 (단위:천원)	구분	연구기간	계	국립 암센터	기업부담금		
					소계	현금	현물
	계	2011.2~2013.12	250,000	250,000			
	제1차	2011.2~2011.12	50,000	50,000			
	제2차	2012.1~2012.12	100,000	100,000			
	제3차	2013.1~2013.12	100,000	100,000			
참여기업	명칭		전화		FAX		
기관고유연구사업관리규칙에 따라 본 연구개발사업을 성실히 수행하였으며 아래와 같이 최종보고서를 제출합니다. 2013년 10 월 30 일 과제책임자 (서명)							
국립 암 센터 원 장 귀 하							
(첨부서류)							

작성요령

- 반드시 편집순서에 따라 작성하여야 함
- 전년도 연차실적을 포함하여 전체 사업기간에 대한 연구결과와 성과를 중심으로 기술함
- 필요한 경우 소제목을 설정하여 체계적인 형식을 갖추도록 함
- 요약문은 연구목표, 연구내용 및 방법, 연구성과 등을 중심으로 작성함
- 요약문중 중심단어(key words)는 5개 이내로 반드시 기재해야 함
- 번호나 기호를 사용한 보고서 형태로 작성하고 표나 그림을 이용할 수 있음. 단, 동 보고서와 함께 제출하는 전산파일에도 같은 표와 그림이 첨부되어 있어야 함

목 차

< 요약 문 >

(한글)

(영문)

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3. 연구결과 고찰 및 결론
4. 연구성과 및 목표달성도
5. 연구결과의 활용계획
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7. 첨부서류

※ 여러개의 세부과제로 과제가 구성된 경우 위 목차와 동일하게 세부과제별로 작성함
(I. 총괄과제, II. 제1세부과제, III. 제2세부과제.....)

< 요약 문 >

<p>연구목표 (200자 이내)</p>	<p><최종목표></p> <p>조기위암환자에서 감시림프절생검을 통하여 림프절전이를 확인하고 그 결과에 따라 전이가 없는 대부분의 환자에서는 비침습적 장기보존수술을 시행함으로써 표준수술인 복강경수술군과 비교하여 동등한 재발율을 유지하면서 수술후 합병증 및 사망률의 단기적 성적을 향상하고 식이 영양등의 장기적 삶의 질 향상.</p> <p><당해연도목표></p> <p>복강경 감시림프절생검 이용 위보존수술의 3상 무작위배정 연구에 참여하는 145명 환자 등재. 정도관리가 완성되어 3상연구에 참여할수 있는 기관을 10개 이상으로 증대.</p>												
<p>연구내용 및 방법 (500자 이내)</p>	<ul style="list-style-type: none"> - 적응증; 내시경 및 CT에서 림프절 전이가 의심되지 않는 점막, 점막하층 및 근육층 (T1) 내에 국한된 직경 3cm 이하의 위암으로 진단된 경우. 점막내 위치한 2cm 이하의 분화암은 제외함. 종양의 위치가 위식도 접합부, 위십이지장 접합부로부터 최소 2cm 이상의 간격이 있는 경우로 함. - 대상환자 580명에 대하여 eVelos를 이용한 무작위배정(표준수술군 vs 감시림프절생검 및 위보존수술군) - 표준수술군; LADG, LATG, LAPG, LAPPG - 감시림프절생검 및 위보존수술군; 전신마취하 수술중 내시경을 이용하여 원발병소를 확인하고, 내시경용 주사기를 이용하여 99mTc-HSA (2ml, 0.1 mCi/ml) 와 ICG (2ml)을 혼합하여 4ml 를 원발종양 주위 한군데 1ml 씩 4군데 점막하에 주사함. 주사 15분후에 색소에 염색된 림프절 및 동위원소를 흡입한 방사능 림프절을 육안 및 복강경용 감마 probe를 이용하여 Sentinel Basin (SB)을 확인함. 복강경을 이용하여 SB을 절제한후 체외로 배출하여 Back table에서 확인하고 Sentinel Basin Nodes (SBN) 를 추출함. 검출된 모든 SBN는 frozen section을 시행. 한 개의 림프절당, 장축의 한면에 대하여, HE stain을 시행하여 확인함. - SBN 전이 확인된 경우는 표준수술시행하고, 전이음성인 경우 위보존수술 (ESD, LGWR, EFTR, LGSR) 시행함. - 수술후 3년간의 경과관찰하여 primary endpoint 인 3yDFS 비교하고, secondary endpoint 인 수술후 morbidity and mortality, QOL 비교함. 												
<p>연구개발에 따른 기대성과</p>	<p><정량적 성과¹⁾></p> <table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr> <th style="width: 33%;">구분</th> <th style="width: 33%;">달성치/목표치¹⁾</th> <th style="width: 33%;">달성도(%)</th> </tr> </thead> <tbody> <tr> <td>SCI 논문 편수</td> <td>6/5</td> <td>120</td> </tr> <tr> <td>IF 합</td> <td>14.81/20</td> <td>74</td> </tr> <tr> <td>기타 성과</td> <td>추가논문 심사중</td> <td>100% 이상 달성예정</td> </tr> </tbody> </table> <p>1) 총연구기간 내 목표연구성과로 기 제출한 값</p> <p><정성적 성과></p> <p>- 2013년 10월까지 18개 기관에서 본 다기관 연구에 참여하고 있으며, 7개 기관에서 3상 연구를 위한 정도관리 연구를 완성한 상태임. 현재까지 4개 기관에서 61명의 3상 연구환자를 등재하여 진행중임.</p>	구분	달성치/목표치 ¹⁾	달성도(%)	SCI 논문 편수	6/5	120	IF 합	14.81/20	74	기타 성과	추가논문 심사중	100% 이상 달성예정
구분	달성치/목표치 ¹⁾	달성도(%)											
SCI 논문 편수	6/5	120											
IF 합	14.81/20	74											
기타 성과	추가논문 심사중	100% 이상 달성예정											

		- 국내외의 다양한 학술대회에서 심포지움, 구연 및 포스터 등을 통하여 본 연구에 대하여 많은 발표를 하였음. 국립암센터 주도의 다기관 공동연구인 감시림프절연구의 중요성을 인지하고 있으며, 향후 지속적인 연구결과에 주목하고 있음.		
색인어	국문	조기위암	감시림프절생검	위보존수술
	영문	early gastric cancer	sentinel node biopsy	stomach preserving surgery

※ 요약문의 총분량은 2page 이내로 제한함

Project Summary

Title of Project	Multicenter phase III trial of sentinel node biopsy based minimally invasive organ preserving surgery in early gastric cancer patients
Key Words	early gastric cancer, sentinel node biopsy, stomach preserving surgery
Project Leader	Keun Won Ryu, MD, PhD.
Associated Company	
<p>The aim of this study is to improve the short-term postoperative complication and long-term QOL without hampering the survival in early gastric cancer patients by the minimal invasive laparoscopic stomach preserving surgery combined with sentinel node biopsy (SNB).</p> <p>The indication is the EGC less than 3cm regardless of histology except absolute indication of ESD. Eligible 580 patients will be randomized to standard surgery group vs. SNB group by the eVelos system. Surgical option for standard group include LADG, LATG, LAPG, LAPPG and SNB group include ESD, LGWR, EFTR and LGSR. During the operation sentinel basin (SB) was identified and dissected after the endoscopic injection of 99mTc-HSA (2ml, 0.1 mCi/ml) and ICG (2ml). After confirmation of SBN metastasis by frozen section, stomach preserving surgery was done if free of metastasis. Standard surgery should be done if the metastatic SNB confirmed. Three years DFS as a primary endpoint will be compared between two randomized groups and the complication and QOL as the secondary endpoint.</p> <p>Six articles acknowledged of the grant number were published and three more papers are under review. Currently 18 institution are involved in the study and 7 institution are finished the quality control study which is prerequisite for the participation of phase III trial. Until now 61 patients are enrolled in phase III trial by 4 institutions. A lot of presentations about this study was done in form of symposium, oral and poster in various international and domestic medical congress. Academic societies are looking for the ongoing status and the final result of this study.</p>	

※ 연구목표, 연구방법, 연구성과를 영문으로 요약하여 2쪽이내의 분량으로 작성

1. 연구의 최종목표

- 당초 연구계획을 참고하기 위한 자료임. 선정당시 「과제계획서」와 전년도 제출하였던 「연구차실적·계획서」상의 내용과 동일하게 작성해야 함. 연구사업의 목적, 범위 등에 대해 기술

조기위암환자에서 감시림프절생검을 통하여 림프절전이를 확인하고 그 결과에 따라 전이가 없는 대부분의 환자에서는 비침습적 장기보존수술을 시행함으로써 표준수술인 복강경수술군과 비교하여 동등한 재발율을 유지하면서 수술후 합병증 및 사망률의 단기적 성적을 향상하고 식이 영양등의 장기적 삶의 질 향상.

2. 연구의 내용 및 결과

- 연구의 이론적, 실험적 연구 방법, 연구 내용 및 결과를 객관적으로 기술

가. 내용

A. 적응증

- 수술이 가능한 전 연령을 대상으로 하며, 심각한 심혈관계, 호흡기계 기능저하 등의 위암요소가 없는 환자이어야 함.
- 수술전 내시경 및 생검에서 위선암으로 증명되고, 내시경 초음파 및 복부 CT에서 림프절 전이가 의심되지 않는 점막 및 점막하층내에 국한된 직경 3cm 이하의 조기위암으로 진단된 경우. 이들중 점막내 위치한 2cm 이하의 분화암은 내시경점막하절제술의 절대적응증 임으로 제외함. 또한 내시경 위부분절제술을 용이하게 하기 위하여 위식도 접합부, 위십이지장 접합부로부터 최소 2cm 이상의 간격이 있는 경우로 함.
- 국립암센터의 경우 상기 적응증에 해당하는 경우는 매년 약 200여명에 달하며, 이들에서의 림프절 전이 빈도는 9.3%임.

B. 감시림프절 생검 방법

- 전신마취하 복강경 수술을 위하여 Troca 설치후, Trietz ligament 직하방의 공장을 복강경용 장감자를 이용하여 clamping함.. (내시경시술중 주입되는 공기의 소장내 유입을 방지함)

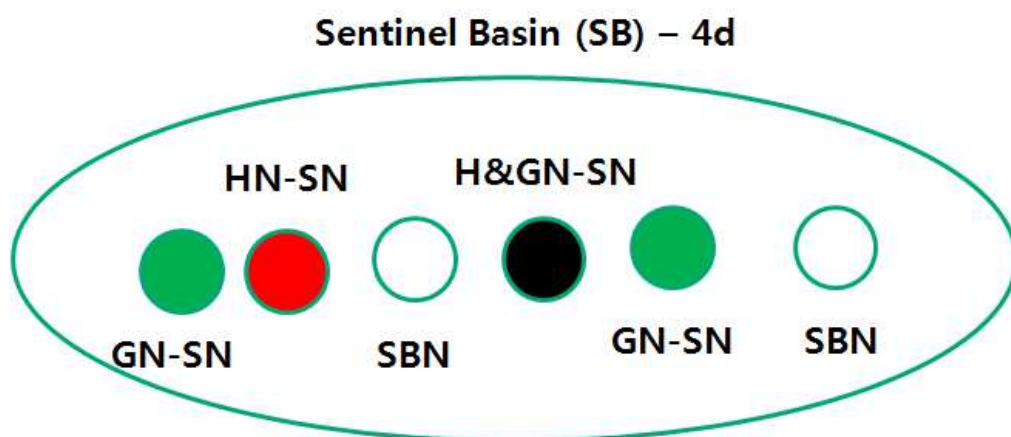
- 수술중 내시경을 이용하여 원발병소를 확인하고, 내시경용 주사기를 이용하여 추적자를 원발종양 주위 4군데 점막하에 주사함.
- 추적자는 99mTc-Human Serum Albumin (2ml, 0.1 mCi/ml) 와 Indocyanin green (2ml)을 혼합하여 4ml 로 준비하여 한군데 1ml 씩 4군데 점막하 주사함.
- 추적자 주사 15분후에 색소에 염색된 림프절 및 동위원소를 흡입한 방사능 림프절을 육안 및 복강경용 감마 probe를 이용하여 Sentinel Basin (SB)을 확인함. Sentinel basin 의 경계는 색소 및 동위원소에 확인되는 거리까지로 정의함.
- 복강경을 이용하여 sentinel basin을 절제한 후 체외로 배출하여 Back table에서 수술자가 확인하여 Senitnel Basin Nodes (SBN) 를 추출함.
- Sentinel basin nodes 는 다음과 같이 표시함.

표시방법 예) 3GN - 3번 station sentinel basin 의 green nodes

4dHN - 4d번 station sentinel basin 의 hot nodes

6GHN - 6번 station sentinel basin 의 green and hot nodes

8BN - 8번 station sentinel basin 의 non green, non hot basin nodes



C. 감시림프절의 병리학적 검사 방법

- 검출된 모든 sentinel basin nodes 들을 frozen section을 시행함. 절제된 감시림프

절에 대해서는 4mm 이하인 경우 수술중 동결절편 한면을 HE염색으로 시행함. 4mm 이상인 경우 2면을 시행하여 미세전이를 진단할수 있도록 함. 동결조직검사전이 음성일 경우 영구조직검사에서 HE염색 2단면과 cytokeratin IHC 1단면 염색 추가함.

D. 감시림프절 전이 음성의 경우 원발종양에 대한 치료

- 수술전 검사와 수술후 병리검사의 차이를 고려하여 아래의 표와 같이 시술함. 각 참여기관의 사정상 하위치료가 불가능할 경우, 상위 치료방법은 허용되나, 하위치료방법은 허용되지 않음.

	mucosa		submucosa	
	≤ 20 mm	20 mm < ≤ 30 mm	≤ 20 mm	20 mm < ≤ 30 mm
Diff	Exclusion	ESD (LGWR, EFTR) (LASR)	LGWR, EFTR (LASR)	LASR
Undiff	ESD (LGWR, EFTR) (LASR)	LASR	LGWR, EFTR (LASR)	LASR

ESD Endoscopic Submucosal Dissection

LGWR Laparoscopic Gastric Wedge Resection

EFTR Endoscopic Full-Thickness Resection

LASR Laparoscopy Assisted Segmental Resection

E. 절제된 원발종양에 대한 병리학적 검사 방법

- 수술중 내시경점막절제술 (ESD) 검체에 대한 동결조직검사 방법은 정확도가 떨어지고, 향후 영구조직검사에 방해 요소로 작용함으로, 수술중 병리검사는 시행하지 않음. Laparoscopic gastric wedge resection (LGWR), Laparoscopic gastric segmental resection (LGSR) 에 대해서는 기존의 표준 수술방법과 동일하게 각 단단면의 종양침

범여부를 수술중 동결 조직 검사방법으로 시행함.

F. 병리검사후 재수술의 기준

- 감시림프절 검사에 대하여 영구조직검사 및 IHC 시행상에서 2mm 이하의 미세전이
의 occult metastasis 가 발견되는 경우 재수술을 시행하지 않음. 그러나, 2mm 이상의
전이가 발견되는 경우는 재수술을 시행하여 복강경을 이용한 표준수술을 시행하는 것
을 원칙으로함.
- 원발종양 절제 병리검사에서, deep and lateral margin 침윤시 재수술을 시행하여
복강경을 이용한 표준수술을 시행하는 것을 원칙으로함.

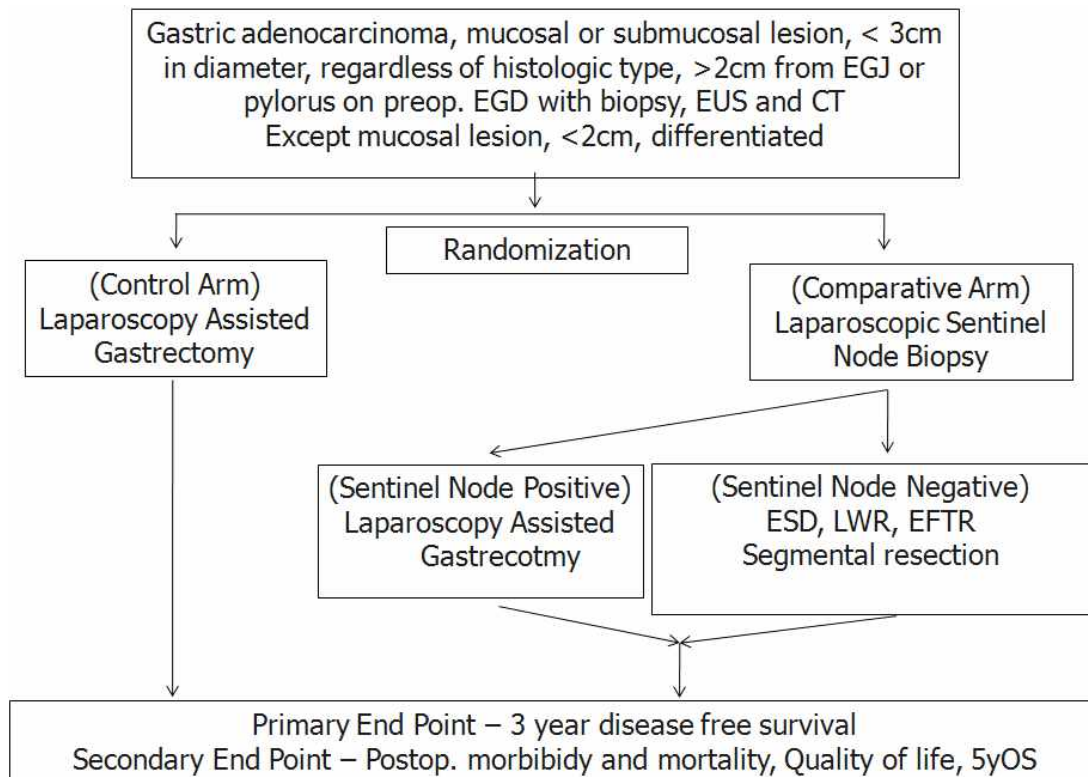
G. 수술후 추적관찰

- 수술후 첫 3개월에 내시경, 6개월 CT, 1년에 내시경, CT 시행하며 이후 2년째까지
매 6개월 간격으로 내시경 및 CT.시행함. 이후 5년까지 1년 간격으로 내시경 및 CT.
시행함.
- 추적관찰기간중 재발이 발견되는 경우, 원격전이가 아닌 경우, 수술적 치료를 원칙
으로 함. 원격전이를 동반한 경우, 기관별 다학제적 토의를 통하여 치료방침 결정함.
- Primary end point 3년 무병생존율임으로, 최소 3년간의 추적관찰이 필요함.
- Secondary end point 5yr Overall survival을 위하여 추적관찰기간은 5년까지 시행
함.

	Preop	1m	3m	6m	1y	1y6m	2y	2y6m	3y	3y6m	4y	4y6m	5y
EGD	*		*	*	*	*	*		*		*		*
CT	*			*	*	*	*		*		*		*
Lab	*	*	*	*	*	*	*	*	*	*	*	*	*
QOL	*	*		*	*		*		*				*

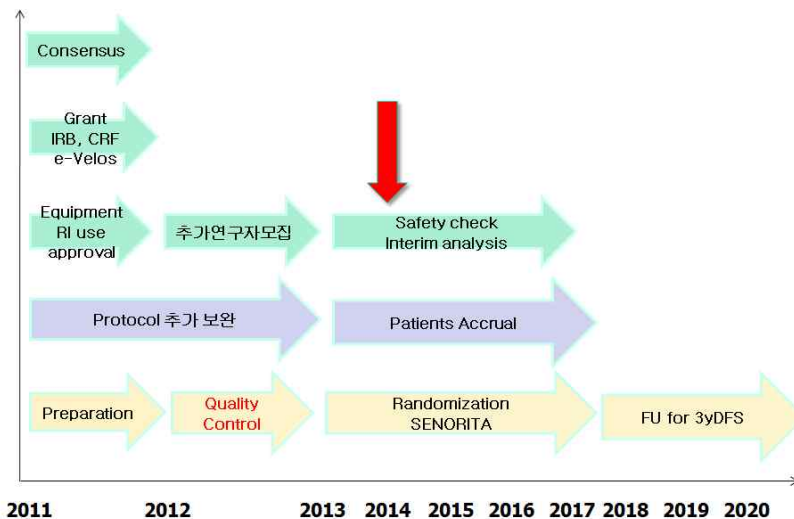
F. 통계학적 고려

- Primary end point 는 3년 무병생존율이며, secondary end point 는 postoperative morbidity and mortality, quality of life 그리고 5년 overall survival 임. 본 연구는 non inferior study design 으로 표준수술군에서의 기대되는 3yDFS는 97%로 예상되며, non-inferior margin을 92%로 하며, alpha error 0.05, power 0.8로 하면 각 군당 261명의 환자가 필요하며 10%의 follow-up loss 를 고려하면 각군당 각각 290명이 필요함. 환자등재는 4년간으로하고 3년 경과 관찰하는것을 목표로함.
- 최대한 환자 등재기간을 단축할수 있도록 추가적인 공동연구자 확보함.
- 본연구의 안전성에 대한 한 검증(Safety analysis)는 각군 50명 등재후 수술후 합병증 및 사망률을 Independent data managing center (IDMC)에 보고하고 검증 받을 계획임. 연구 진행 여부는 IDMC 의 권고사항에 의하여 결정함.
- 또한 1/3 등재환자의 3년 무병생존율이 보고되는 시점에서 Interim analysis 를 시행하여 safety analysis 와 같은 방식으로 IDMC에 보고하고 검증받을 계획임.



나. 결과

- 2011년 2월부터 18개 기관이 참여하는 다기관 3상연구의 protocol 개발, standardization, workshop, seminar, symposium 진행하여 공동연구자들간의 consensus 개발함.
- 2012년부터 다기관 3상연구를 위한 quality control study를 진행하여, qualified institution 에 한하여 3상연구를 진행하는 것으로 결정하고, 현재까지 7개 기관에서 107 명의 환자를 대상으로 71명의 환자에서 quality control을 완성하였음. Quality control 107명에 대한 결과 분석은 현재 진행중임.
- 2013년부터 quality control 완성된 기관에서 3상연구환자에 대하여 등재와 수술을 시행하고 있으며, 2013년 10월까지 quality control 연구를 완성한 7개 기관중 4개 기관에서 61명의 3상 연구환자를 등재하여 진행중이며, 나머지 3개 기관에서도 3상 환자 등재 예정임.
- 3상 등재환자 50명에 대하여 수술이 시행되고 한달 경과후, independent monitoring committee (IDMC)에 safety analysis 보고 후 연구 진행여부에 대하여 승인 예정임.
- 국내외의 다양한 학술대회에서 심포지움, 구연 및 포스터 등을 통하여 본 연구에 대하여 많은 발표를 하였음. 국립암센터 주도의 다기관 공동연구인 감시림프절연구의 중요성을 인지하고 있으며, 향후 지속적인 연구결과에 주목하고 있음.



3. 연구결과 고찰 및 결론

- 국내·외 관련분야의 기술개발 현황과 연구결과가 국내·외 기술개발 분야에서 차지하는 위치 등을 기술
- 연구결과 해석 및 다른 결과와의 비교분석 등에 대해 고찰하고 결론을 서술함

- 공동연구자들에 의하여 개발된 프로토콜에 의하여 원활히 진행되고 있음.
- Quality control 연구 결과는 현재 분석중이며, 3상 연구에 대한 결과는 초기 등재환자 50명을 대상으로 수술후 합병증을 분석할 예정임.
- 3상연구의 최종 결과인 3yDFS, postoperative morbidity and mortality, QoL 에 대해서는 연구대상환자 580명 등재후 최소 3년간의 경과 관찰후 결과 분석 예정임.
- 일본의 Kitagawa 등은 다기관 feasibility 연구 결과를 발표하고 이를 바탕으로 3상연구를 준비중임. Primary end point 는 5-year recurrence-free survival rate 이며, 3-year recurrence-free survival, 3- to 5-year overall survival, diagnostic accuracy of SNs, and postoperative quality of life 등을 secondary end points 로 연구 준비중임.
- 일본에서 다기관 3상 연구가 진행될 경우, 본 연구와 함께 국제적으로 경쟁적인 다기관 3상연구 구도 전망됨.

4. 연구성과 및 목표달성도

(1) 연구성과

- 과제시작시점부터 과제종료시점까지의 연구성과(학술지 게재, 학회발표, 학위논문, 산업재산권 출원·등록, 워크샵 또는 심포지움 개최, 전시회 참가, 임상응용, 기술성과 이전, 벤처 창업 등의 실적)를 기재하되, 본 과제와 관련성이 있는 성과에 한하여 기재
※ 논문, 특허성과는 과제 시작시점이후 게재 신청 또는 출원된 실적만 기재.

가. 국내 및 국제 전문학술지 논문 게재 및 신청

논문명	저자 (저자구분 ¹⁾)	저널명(I.F.)	Year; Vol(No):Page	구분 ²⁾	지원과제번호 ³⁾
Is the new seventh AJCC/UICC staging system appropriate for patients with gastric cancer?	류근원 (교신)	BRIT J SURG (4.606)	2012;214(1):8 8-96	국외 SCI	1110550
Prognostic significance of peritoneal washing cytology in patients with gastric cancer.	류근원 (교신)	J AM COLL SURGEONS (4.549)	2012;99(3):39 7-403	국외 SCI	1110550
The future of sentinel node oriented tailored approach in patients with early gastric cancer.	류근원 (교신)	J Gastric Cancer ()	2012;12(1):1-2	국내	1110550
Future perspective of laparoscopic surgery for gastric cancer: Sentinel node navigation function-preserving surgery for early gastric cancer	류근원 (교신)	Transl Gastrointestin Cancer ()	2013;2(3):160- 163	국외	1110550
The risk factors for lymph node metastasis in early gastric cancer patients who underwent endoscopic resection: Is the minimal lymph node dissection applicable?:A retrospective study.	류근원 (교신)	SURG ENDOSC (3.427)	2013;27(9):32 47-3253	국외 SCI	1110550
Prognostic impact of microscopic tumor involved resection margin in advanced gastric cancer patients after gastric resection.	류근원 (교신)	WORLD J SURG (2.228)	online published	국외 SCI	1110550
Proposal of the surgical options for primary tumor control during sentinel node navigation surgery based on the discrepancy between preoperative and postoperative early gastric cancer diagnosis	류근원 (교신)	ANN SURG ONCOL (4.12)	under review	국외 SCI	1110550
Robot-assisted gastrectomy for early gastric cancer: which patients would benefit from robotic surgery compared to laparoscopic approach?	류근원 (교신)	BRIT J SURG (4.839)	under review	국외 SCI	1110550
Survival nomogram in curatively resected Korean gastric cancer	류근원 (교신)	ANN SURG (6.329)	under review	국외 SCI	1110550

patients; Multicenter retrospective analysis with external validation.					
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- 1) 저자구분 : 교신, 제1, 공동
- 2) 구분 : 국내, 국내 SCI, 국내 SCIE, 국외, 국외SCI, 국외SCIE 등
- 3) 지원과제번호(Acknowledgement)
 - 과제번호를 연차 표시(-1, -2, -3 등)를 생략하고 7자리로 기재하고, 과제와 관련성은 있으나 불가피하게 Acknowledgement가 누락된 경우에는 '없음'으로 기재

나. 국내 및 국제 학술대회 논문 발표

논문명	저자	학술대회명	지역 ¹⁾	지원과제번호
Is the new 7 th UICC/AJCC staging system appropriate for patients with gastric cancer?	윤홍만, 류근원	9 th International Gastric Cancer Congress	국내	1110550
Oncologic effectiveness of regular follow-up to detect recurrence after the curative resection of gastric cancer.	엄방울, 류근원	9 th International Gastric Cancer Congress.	국내	1010490
Comparison of surgical performances and short-term clinical outcomes between laparoscopic and robotic surgery in gastric cancer.	엄방울, 류근원	20 th International Congress of the European Association for Endoscopic Surgery	국외	1010490
Biopathologic features and clinical significance of micrometastasis in the lymph node of early gastric cancer.	박지연, 류근원	10 th International Gastric Cancer Congress	국외	0910560 1010490
The risk factors for lymph node metastasis in early gastric cancer patients who underwent endoscopic resection: Is the minimal lymph node dissection applicable?	박지연, 류근원	10 th International Gastric Cancer Congress	국외	1110550
Proposal of the surgical options for primary tumor control during sentinel node navigation surgery based on the discrepancy between preoperative early gastric cancer diagnosis.	박지연, 류근원	10 th International Gastric Cancer Congress	국외	1110550

1) 지역 : 국내, 국외

다. 산업재산권

구분 ¹⁾	특허명	출원인	출원국	출원번호

1) 구분 : 발명특허, 실용신안, 의장등록 등

라. 저 서

저서명	저자	발행기관(발행국, 도시)	쪽수	Chapter 제목, 쪽수 (공저일 경우)
Laparoscopic Gastrectomy for Cancer - Standard Techniques and Clinical Evidences.	Keun Won Ryu, Woo Jin Hyung, Nobuhiko Tanigawa, Sang-Woon g Lee.	Springer, 2012	101-104	Role of Robotic Surgery for Laparoscopy-Assisted Distal Gastrectomy.
Laparoscopic Gastrectomy for Cancer - Standard Techniques and Clinical Evidences.	Hirokazu Yamaguchi, Michio Kaminishi, a n d KeunWonRyu.	Springer, 2012	163-164.	Training Systems and the Learning Curve. In Laparoscopic Gastrectomy for Cancer - Standard Techniques and Clinical Evidences.

마. 연구성과의 정부정책 기여

보고서명	정부정책	기여내용

바. 기타연구성과

(2) 목표달성도

가. 연구목표의 달성도

- 사업목표에 대한 달성내용 및 관련분야 기술발전예의 공헌도 등을 기술
- 달성도(%)는 연차별목표대비 당해연도 달성도 및 최종목표대비 당해연도까지의 누적 달성도를 반드시 기입

최종목표	연차별목표	달성내용	달성도(%)	
			연차	최종
등재목표 양군 각각 290 명 등재 및 추적관찰 후 3년 무병생존율, 수술후 이환율, 사망률, 삶의	1차년도	다기관 다학제적 공동연구자들간의 consensus 형성되었으며, 이를 바탕으로 한 Protocol 개발하였음. 3상연구를 위한 Quality control 연구는 차기연도에 시행할 계획임. 이에 따른 IRB 심의예정임.	95%	10%
	각기관별 Retrospective data collection	감시립프절의 data 들은 각기관별로 이미 논문으로 보고되어 있는		

질 비교			상태로, 전체적인 후향적 연구는 시행하지 못하였음.		
	2차년도	정도관리 성취된 기관의 최대화	7개 공동연구 기관에서 환자 등재	90%	20%
		정도관리 성취를 위한 학습곡선에 대한 연구	현재 정도관리를 완성한 기관이 없음으로, 차기 년도 분석 예정		
	3차년도	복강경감시림프절 생검 정도관리참여 10개기관 이상	현재 7개 기관 완성	90%	30%
복강경 감시림프절 생검 3상연구 145명 등재		10월 현재 61명 등재			

나. 평가의 착안점에 따른 목표달성도에 대한 자체평가

평가의 착안점	자 체 평 가
참여예정 14개 기관과 추가 참여기관중 최소 10개 기관 이상을 정도관리연구 참여목표로 함.	본 연구 참여기관을 18개로 증대하였으나, 연구에 필요한 감마프로브 각 기관별 구입문제와 다학제적 연구 인프라 부족 등으로 정도관리 연구시작 기관을 10개로 증대하기는 현실적인 한계점이 있음.
10중례의 완성된 정도관리 기관에서 경쟁적 등재를 통하여 목표달성.	정도관리 연구를 마친 7개 기관중 현재 4개 기관에서만, 3상 환자를 61명 등재였음. 지속적인 4개 기관 등재와, 향후 나머지 3개 기관에서 추가적인 등재하게 되면, 연구종료시점인 12월 까지는 하여 약 100명 정도의 3상 연구환자 등재 가능할것으로 사료됨.

5. 연구결과의 활용계획

(1) 연구종료 2년후 예상 연구성과

<ul style="list-style-type: none"> ○ 연구종료 2년후까지 연구사업 결과로 발생할 것으로 예상되는 성과, 즉 학술지 게재, 산업재산권 등을 단계별로 다음의 양식에 의거하여 작성함. 학술지 게재는 게재 예상 학술지 명과 Impact Factor 등을 기재함 ○ 연구사업의 내용이 논문이나 산업재산권과 연결되기 힘든 과제인 경우, 자유 형식으로 예상연구성과 및 활용정도를 기재하되 최대한 계량화할 것 <p>예) DB 몇 건 구축완료. OOO 시스템 구축 및 OO사업 완료</p>
--

구 분	건 수	비 고
학술지 논문 게재	3	ANN SURG ONCOL(4.12) BRIT J SURG (4.839) ANN SURG (6.329)
산업재산권 등록		특허 등록 예상 국가, 예상 특허명 등
기 타		

(2) 연구성과의 활용계획

- 연구성과물의 활용분야 및 활용방법, 활용범위 등을 구체적(특히 시간적 구체성, 예를 들어 몇 년 안에 치료기술 실용화 등)으로 기술하되, 참여기업이 포함되어 있는 과제인 경우 기업과 연계한 활용방안에 대해서도 기술함
- 추가 후속연구의 필요성에 대해서도 간략하게 기술함

- 본 기관고유연구는 다기관 3상 연구방법으로 표준수술군과 감시림프절 수술군 양군 580명을 4년간 등재후 최소 3년 경과관찰후 primary endpoint 및 secondary endpoint 분석예정임.

- 현재까지 protocol 개발, standardization 그리고 quality control 연구 등을 기반으로 1년간의 3상 환자를 등재하였음. 따라서 향후 약 3년간의 3상 환자 등재기간과 3년간의 경과관찰의 연구기간이 추가적으로 필요함.

- 본 3상연구 종료후 연구결과에 따라서 향후 조기위암환자에서는 기존의 위절제술 대신 감시림프절생검 및 위부분절제를 시행하여 생존율을 동일하게 유지하면서 장기 생존하는 조기위암환자의 삶의 질을 개선할 수 있는 패러다임의 변화를 가져올 것으로 기대됨.

6. 참고문헌

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7. 첨부서류

○ 본 연구의 성과로 논문, 저서, 산업재산권, 정책정책 기여 등이 있을 경우 관련 증빙자료를 첨부토록 함

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Prognostic significance of peritoneal washing cytology in patients with gastric cancer

S. D. Lee¹, K. W. Ryu², B. W. Eom², J. H. Lee², M. C. Kook² and Y.-W. Kim²

¹Department of Surgery, Seoul National University College of Medicine, Seoul, and ²Gastric Cancer Branch, Research Institute and Hospital, National Cancer Centre, Goyang, Korea

Correspondence to: Dr K. W. Ryu, Gastric Cancer Branch, Research Institute and Hospital, National Cancer Centre, 323 Ilan-ro, Ilсандong-gu, Goyang-si Gyeonggi-do, 410-769, Korea (e-mail: docryu@kccr.com)

Background: Positive peritoneal washing cytology is a poor prognostic factor in patients with gastric cancer. The right therapeutic approach for this condition has not been well documented.

Methods: Patients who underwent surgery for gastric cancer with suspected serosal invasion and peritoneal washing cytology at the Korean National Cancer Centre between May 2001 and December 2009 were included in this retrospective study. Clinicopathological factors and overall survival were analysed with respect to the cytological results and presence of peritoneal metastases. Prognostic factors were analysed in patients with positive cytology but without overt peritoneal metastases.

Results: A total of 1072 patients were included in the analysis, of whom 900 had negative cytology (C0 group) and 172 had positive cytology (C1 group). No peritoneal metastases (P0) were found in 830 patients (92.2 per cent) in the C0 group. Peritoneal metastases (P1) were found in 76 patients (44.2 per cent) in the C1 group. Median overall survival times in the P0 C1, P1 C0 and P1 C1 subgroups were 20.0, 14.0 and 10.0 months respectively. Multivariable analysis of the P0 C1 subgroup revealed that clinical N0–2 category and gastric resection were significantly associated with better prognosis (median survival 24.0 *versus* 13.0 months for N0–2 *versus* N3, and 21.0 *versus* 4.0 months for resected *versus* non-resected).

Conclusion: Positive washing cytology in patients with gastric cancer is a negative prognostic factor for patients with, as well as those without, overt peritoneal metastases. Resection is an option in patients with clinical stage N0–2 disease without peritoneal metastases but with a positive washing cytology finding.

Paper accepted 20 October 2011

Published online 18 November 2011 in Wiley Online Library (www.bj.s.co.uk). DOI: 10.1002/bjs.7812

Introduction

Gastric cancer is the most common cancer in South Korea (53.7 per 100 000 population) and the third most frequent cause of cancer death in Western countries^{1–3}. Survival has been improved by early endoscopic surveillance, and medical and surgical advances^{4,5}. The prognosis is favourable in early gastric cancer following appropriate treatment^{6,7}, but many patients continue to present with advanced disease. Here, the prognosis is poor despite multimodal therapy⁸.

Peritoneal metastases are the most common type of metastasis in patients with advanced gastric cancer⁹. The prognosis of patients with peritoneal metastases is dismal

and median survival is only months. In addition to overt metastases, positive peritoneal washing cytology has been shown to predict peritoneal metastases and recurrence. Positive peritoneal washing cytology is included in the American Joint Committee on Cancer (AJCC) staging system (7th edition) as M1 disease¹⁰. For this reason, peritoneal washing cytology of the abdominal cavity is obtained during gastric cancer surgery at many institutions^{11,12}.

However, it is difficult to view positive peritoneal washing cytology in the absence of overt peritoneal metastases as M1 disease, because prolonged survival has been reported in this situation. Furthermore, although many retrospective studies have been conducted on

Is the New Seventh AJCC/UICC Staging System Appropriate for Patients with Gastric Cancer?

Hong Man Yoon, MD, Keun Won Ryu, MD, Byung Ho Nam, MD, Soo Jeong Cho, MD, Sook Ryun Park, MD, Jong Yeul Lee, MD, Jun Ho Lee, MD, Myeong-Cherl Kook, MD, Il Ju Choi, MD, Young-Woo Kim, MD

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- BACKGROUND:** The purpose of this study was to compare the clinical usefulness of the seventh Union Internationale Contre le Cancer/American Joint Committee on Cancer (AJCC/UICC) staging system vs the sixth AJCC/UICC staging system in patients with gastric cancer.
- STUDY DESIGN:** Included were 1,799 patients who underwent surgery for gastric cancer between January 2001 and June 2005 at the National Cancer Center (South Korea). For the sixth and seventh AJCC/UICC staging systems, survival outcomes stratified by stage, by T classification, and by N classification were summarized using Kaplan-Meier curves and compared statistically using a log rank test; survival differences were quantified using hazard ratios estimated from a Cox regression model. The 2 systems were compared in terms of prognostic performances using the linear trend chi-square test, likelihood ratio chi-square test, and Akaike information criterion (AIC) in the Cox regression analysis.
- RESULTS:** Significant survival differences between each stage were not found using the seventh staging system, especially for stages IB, IIA, and IIB ($p = 0.14$ and $p = 0.11$). The sixth staging system had higher linear trend chi-square score and likelihood ratio chi-square score, which means better discriminatory ability, monotonicity, and homogeneity, and had smaller AIC, which indicates better optimistic prognostic stratification, especially in the N classification. The modified staging system combining the T classification of the seventh AJCC/UICC system and the N classification of the sixth system showed better prognostic performance compared with each separate version (sixth or seventh) of the staging system.
- CONCLUSIONS:** The seventh AJCC/UICC staging system is not more clinically useful than the sixth system in surgically treated patients with gastric cancer because of an inappropriate N classification. A new TNM system is required with a different N classification. (*J Am Coll Surg* 2012;214: 88–96. © 2012 by the American College of Surgeons)
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Cancer staging is an essential element of modern oncology and is used for creating, disseminating, and applying knowledge to the care of individual patients, and to the management of cancer control programs.¹ Therefore, correct staging is important.² In particular, staging systems are important in gastric cancer, because preoperative stage,³

intraoperative stage,⁴ and pathologic stage are important factors for determining neoadjuvant and adjuvant therapy and intraoperative surgical strategy. Furthermore, Asian and Caucasian gastric cancer patients have different clinicopathologic characteristics.⁵

In gastric cancer, the major change made in the fifth American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) staging system as compared with the fourth staging system was the introduction of an N classification based on the number of metastatic lymph nodes.⁶ Recently, T and N classifications in the seventh AJCC/UICC staging system were substantially changed as compared with the sixth staging system. This seventh staging system for gastric cancer appears to be similar to those of the seventh staging systems for colorectal cancer and esophageal cancer.⁷ This unification of staging systems may help physicians understand the complexities

Disclosure Information: Nothing to disclose.

Support: This study was supported from a grant from the National Cancer Center (grant no. 1110550).

Received April 5, 2011; Revised September 21, 2011; Accepted September 21, 2011.

From the Gastric Cancer Branch, Research Institute and Hospital (Yoon, Ryu, Cho, Park, JY Lee, JH Lee, Kook, Choi, Kim) and the Center for Clinical Trials, National Cancer Center (Nam), Gyeonggi-do, Korea.

Correspondence address: Keun Won Ryu, MD, Gastric Cancer Branch, Research Institute & Hospital, National Cancer Center, 809 Madu-dong, Ilsandong-gu, Goyang-si, Gyeonggi-do, 411-764, Korea. email: docryu@korea.com

The Future of Sentinel Node Oriented Tailored Approach in Patients with Early Gastric Cancer

Keun Won Ryu

Gastric Cancer Branch, Research Institute and Hospital, National Cancer Center, Goyang, Korea

After the introduction of sentinel node biopsy (SNB) concept in early gastric cancer (EGC) more than decade, it is not yet a practically acceptable procedure in the same manner as breast cancer or melanoma.(1-3) In this issue, Dr. Miyashiro critically reviewed the practical problem and current status of SNB in EGC and suggested more sophisticated methods.(4) The debating points made in this review article by Dr. Miyashiro is that which is commonly accepted by the consensus of the surgical society. For the optimistic future of SNB in EGC, several ideas need be shared with researchers throughout the world.

The first consideration is that the protocol of SNB should be universally applicable. A highly standardized protocol of surgical procedure and pathologic evaluation cannot be adopted in all institutions, even with the satisfactory accuracy of SNB. The protocol, which can be done only by a specialized center, is not ideal and we should develop a more practical method that can be performed by a wider range of institutions.(5)

The second consideration is that the end goal of SNB in EGC surgery is the preservation of organ and its function by minimizing lymph node dissection (LND). In contrast, SNB in breast cancer and melanoma is performed to prevent lymphedema by minimizing LND. In the context of SNB, the pick-up method is more appropriate rather than the basin dissection. However, the

pick-up method is somewhat limited in terms of sensitivity in EGC. If we can accurately diagnose the lymph node metastasis and the organ and function preserving surgery by basin dissection, it is the alternative method of pick-up method. In the era of minimally invasive surgery, most of EGC is now operated with laparoscopic surgery and the difficulty of pick up biopsy by laparoscopy should also be considered.(6,7)

The third consideration is the issue of the qualifying involved surgeon, endoscopist, pathologist and institution. The qualification is usually estimated by case number of practice, which serves as a representative of the learning curve.(8) However, the qualification cannot not be estimated merely by the case number because personal and institutional learning curves are different each other and should be measured by somewhat objective protocol.

After two multicenter trials of SNB in Japan, we have invaluable lessons and can prepare for the prevention against defects and problems.(4,9,10) For the confirmation of clinical applicability of SNB in EGC, multicenter phase III trial should be mandatory. Recently, Korean surgical societies are now preparing trials of sentinel node oriented tailored approach (SENRITA trial) comparing the conventional laparoscopic gastrectomy versus laparoscopic SNB, with the organ and function preserving surgery of EGC. Before the randomized controlled trial, a qualification study of participating institutions will be done by measuring the completion of each critical step of SNB protocol.(11)

Several practical obstacles should be corrected by the evidence-based approach for the optimistic future of SNB. For an improved quality of life in the long-term surviving EGC patient, organ and function preserving surgery is essential and indispensable by applying SNB in the future.

Correspondence to: Keun Won Ryu
Gastric Cancer Branch, Research Institute and Hospital, National Cancer Center, 809, Madu 1-dong, Ilsandong-gu, Goyang 410-769, Korea
Tel: +82-31-920-1628, Fax: +82-31-920-0069
E-mail: docryu@korea.com
Received March 5, 2012
Revised March 7, 2012
Accepted March 7, 2012

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The risk factors for lymph node metastasis in early gastric cancer patients who underwent endoscopic resection: is the minimal lymph node dissection applicable?

A retrospective study

Sang Yong Son · Ji Yeon Park · Keun Won Ryu · Bang Wool Eom ·
Hong Man Yoon · Soo Jeong Cho · Jong Yeul Lee · Chan Gyoo Kim ·
Jun Ho Lee · Myeong-Cherl Kook · Il Ju Choi · Young-Woo Kim

Received: 6 September 2012 / Accepted: 15 February 2013 / Published online: 19 March 2013
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Abstract

Purpose The purpose of this study was to identify risk factors associated with lymph node (LN) metastasis in early gastric cancer patients who underwent endoscopic resection (ER) and to evaluate the feasibility of minimal LN dissection in these patients.

Methods From January 2001 to March 2011, patients who underwent gastrectomy with lymphadenectomy due to the potential risk of LN metastasis after ER were enrolled at National Cancer Center, Korea. The incidence, risk factors, and distribution of LN metastasis were evaluated.

Results Of the 147 enrolled patients, the LN metastasis was identified in 12 patients (8.2 %). The incidence of LN metastasis was not significantly increased in patients with submucosal invasion, lymphovascular invasion, and mixed undifferentiated histology [odds ratio (OR), 5.55, 1.349, and 0.387; 95 % confidence interval (CI), 0.688–43.943, 0.405–4.494, and 0.081–1.84, respectively]. Tumor size more than 2 cm was significantly associated with LN metastasis (OR, 14.056; 95 % CI, 1.76–112.267). The incidence of LN metastasis gradually increased from 3.2 to

20 %, as number of risk factors increased ($P = 0.019$). LN metastasis was present primarily along the perigastric area in all except two patients (1.4 %) with skip metastasis to extragastric area.

Conclusions Standard surgery with at least D1 + LN dissection must be recommended for patients who proved to have risk factors for LN metastasis after ER, because the potential of skip metastasis is not negligible. Nevertheless, the minimal LN dissection, such as sentinel basin dissection, might be applied cautiously in patients with small-sized tumors after ER.

Keywords Early gastric cancer · Endoscopic resection · Lymph node metastasis · Skip metastasis

The prevalence of early gastric cancer (EGC) is growing with the advance in diagnostics and screening programs; endoscopic resection (ER) has become an important treatment for selected EGC patients. If there are submucosa (SM) invasion, lymphovascular invasion (LVI), mixture with undifferentiated histology, and large tumor size after ER, surgical treatment should be considered because of the potential risk of lymph node (LN) metastasis. However, the extent of LN dissection is still debated in these patients [1–3]. Because there is a limitation in the ability to predict LN metastasis due to unsatisfactory accuracy of computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS), gastrectomy with LN dissection should be considered in these patients. After this type of surgery, 80–95 % of the patients might not be benefitted, probably due to an absence of LN metastasis, and will suffer from both the short-term postoperative morbidity and worse quality of life in the long term. For these reasons several studies, such as sentinel node biopsy

Sang Yong Son and Ji Yeon Park contributed equally to this study.

S. Y. Son
Department of Surgery, Seoul National University Bundang
Hospital, Seongnam, South Korea

J. Y. Park · K. W. Ryu (✉) · B. W. Eom ·
H. M. Yoon · S. J. Cho · J. Y. Lee · C. G. Kim ·
J. H. Lee · M.-C. Kook · I. J. Choi · Y.-W. Kim
Gastric Cancer Branch, Research Institute & Hospital, National
Cancer Center, 111 Jeongbalsanro, Ilsandong-Gu, Goyang-si,
Gyeonggi-do 410-769, South Korea
e-mail: doeryu@korea.com

J. Y. Park
e-mail: jybak99@hanmail.net

Future perspective of laparoscopic surgery for gastric cancer: sentinel node navigation function-preserving surgery for early gastric cancer

Keun Won Ryu, SENORITA (Sentinel Node Oriented Tailored Approach) Study Group

Gastric Cancer Branch, Research Institute and Hospital, National Cancer Center, Republic of Korea

Corresponding to: Keun Won Ryu, M.D, Ph.D. 809 Madul-dong, Ilsandong-gu, Goyang-si, Gyeonggi-do, 410-769, Republic of Korea. Email: dkeryu@nccrca.com.

Abstract: After the introduction of laparoscopic surgery in gastric cancer, the short-term surgical outcome is improved regarding the quality of life (QOL) with the equivalent morbidity comparing to the conventional open surgery. However, there is controversy concerning the long-term improvement of QOL after laparoscopic gastric cancer surgery. This might be due to the same resection range of stomach and lymph node dissection between laparoscopic surgery and open surgery. To improve the long-term QOL without impairing recurrence and survival in gastric cancer surgery, stomach preserving surgery with minimal lymph node dissection through the laparoscopic approach should be considered without residual tumor in the stomach and surrounding lymph nodes. The sentinel node biopsy (SNB) concept can be adopted for this purpose. The SNB results in terms of sensitivity from individual institutions are unsatisfactory and heterogeneous among practicing surgeons. However, recently performed multicenter study from Japan offers the optimism of SNB in gastric cancer. Currently, SENORITA (Sentinel Node Oriented Tailored Approach) study group in Korea is preparing the phase III trial for stomach preserving surgery with SNB. Before the phase III trial, quality-control study of participating institutions is underway for the standardization and overcoming the learning curve of SNB. If the SNB and stomach preserving surgery can be verified by this phase III trial, it might be a good surgical option instead of standard gastrectomy and lymphadenectomy resulting in improved long-term QOL without hampering the recurrence and survival in the subgroup of early gastric cancer.

Key Words: Early gastric cancer (EGC); sentinel node biopsy; stomach preserving surgery



Submitted Apr 15, 2013. Accepted for publication May 06, 2013.

doi: 10.3978/j.issn.2224-4778.2013.05.02

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Introduction

As the screening program for gastric cancer has been developed in Korea, the proportion of early gastric cancer (EGC) has been increased and the survival from the gastric cancer was improved (1,2). The standard surgical option for these EGC patients is gastrectomy with enough resection margins and the lymph node dissection according to the Japanese guideline except the absolute indication for endoscopic resection (ER) (3). Such surgical treatment makes the survival of EGC increase more than 90% but

the short-term surgical outcomes are still morbid and postoperative quality of life (QOL) was impaired due to the resected stomach and destroyed nerves system during the lymph node dissection. As a consequence, the need for the minimally invasive approach is required for potential long-term survival of EGC.

After the application of laparoscopic surgery in gastric cancer, the short-term surgical outcomes are improved regarding QOL with the equivalent morbidity comparing to the conventional open surgery and the final survival

Prognostic Impact of Microscopic Tumor Involved Resection Margin in Advanced Gastric Cancer Patients after Gastric Resection

Jung-Woo Woo · Keun Won Ryu · Ji Yeon Park · Bang Wool Eom ·
Mi Jung Kim · Hong Man Yoon · Sook Ryun Park · Myeong-Cheri Kook ·
Il Ju Choi · Young-Woo Kim · Young-Iee Park

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Abstract

Background The prognosis of patients with positive surgical resection margins is dismal in gastric cancer. However, the influence of positive margin itself on prognosis is still uncertain, especially in advanced gastric cancer (AGC). The aims of the present study were to evaluate the prognostic impact of microscopic tumor involved resection margins in stage III–IV AGC after gastric resection in comparison with other well-known factors.

Methods Among 1,536 consecutive gastric cancer patients who received intentional curative resection for stage III–IV AGC between April 2001 and December 2011 at the National Cancer Center, 35 patients (2.28 %) had positive resection margins on their final histology. A comparison of clinicopathologic characteristics, recurrence pattern, overall survival (OS), and disease-free survival (DFS) was made between positive margin (PM) patients and negative margin (NM) patients.

Results Among the 35 PM patients, 15 (42.9 %) had proximal involved margins, 21 (60.0 %) had distal involved margins, and one (2.9 %) had both involved margins. Twenty-eight PM patients (80.0 %) were stage III, and 7 (20.0 %) were stage IV. Recurrence was significantly higher in PM than NM (63.6 % vs. 39.7 %,

respectively; $p = 0.005$). The OS and DFS rates were significantly lower in the PM group than in the NM group (14.9 vs. 36.3 months, $p < 0.001$ and 11.6 vs. 27.1 months, $p = 0.005$, respectively). The presence of PM was an independent risk factor for both OS and DFS.

Conclusions The presence of PM is an independent risk factor for OS and DFS. Considering the prognostic impact of PM, a sufficient resection margin should be ensured when determining the resection line in gastrectomy with curative intent. The reoperation to secure clear resection margins should be considered as a treatment of choice in the case of PM.

Introduction

Historically, gastric cancer has been one of the major cancers in East Asian countries, including Korea and Japan. Although the mortality of gastric cancer has decreased in these countries for several reasons, including the introduction of screening programs, it is still the fourth most common cancer in the world and the second most common cancer in Asia and Korea. Globally, gastric cancer accounts for 989,600 new cases and 738,000 deaths annually. The case-fatality ratio of gastric cancer is higher than for other common malignancies, such as colon, breast, and prostate cancers [1–4].

Despite the development of accurate diagnostic techniques, gastric cancer is usually detected in an advanced state because most patients experience vague and nonspecific symptoms in the early stages, and cancer-related symptoms only become noticeable in advanced stages. Standard treatments, such as surgery and chemotherapy, have limited value in advanced disease due to the paucity of molecular markers for targeted therapy. Because cancer of the stomach has a very poor prognosis and the 5-year survival rate is only around 20 % in the world, a new look at the results of

J.-W. Woo (✉)
Department of Surgery, Seoul National University Hospital,
Seoul, Republic of Korea
e-mail: wfriend11@gmail.com

K. W. Ryu · J. Y. Park · B. W. Eom · M. J. Kim ·
H. M. Yoon · S. R. Park · M.-C. Kook ·
I. J. Choi · Y.-W. Kim · Y.-I. Park
Gastric Cancer Branch, National Cancer Center, Madu 1-dong,
Isandong-gu, Goyang 410-769, Republic of Korea
e-mail: doeryu@korea.com